The Examiner objects to the specification under 35 U.S.C. § 132, first paragraph, asserting that the Amendment filed July 19, 1998 introduces new matter. The Examiner contends that the amendments to Tables 2 and 3 are not supported by provisional application no. 60/025,579, filed September 6, 1999, because the instant application does not expressly incorporate by reference the disclosure of the provisional application. The Examiner requires cancellation of the amendments to Tables 2 and 3. Applicants respectfully traverse.

Applicants have amended the specification to claim priority under 35 U.S.C. §120 to U.S. Application No. 60/025,579, which was pending as of the filing date, September 25, 1996, of the instant application. The amendment is supported by the executed Declaration mailed February 26, 1997. Thus, the amendments to Tables 2 and 3, which are entirely based on the provisional application, do not constitute new matter. Applicants respectfully request the Examiner to withdraw the objection.

Claims 4 and 12 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner contends the specification is enabling for antibodies to RET but does not enable other reagents that bind to RET. Applicants respectfully traverse.

With the amendments submitted herein, the term "reagent" has been deleted from Claims 4 and 12 and replaced with "antibody". Applicants respectfully request the rejection be withdrawn.

Claims 1 and 2 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner contends the specification discloses the binding of monoclonal antibodies to cell surface RET as a transient labeling step during cell separation or cell identification but provides no description or guidance for how or why one uses the antibodies themselves for any purpose other than cell labeling. The Examiner concludes the specification does not enable other uses for a monoclonal

Applicants respectfully submit that the Examiner has misinterpreted Claim 1. To resolve the issues surrounding Claim 1 it has been amended but its scope has not been altered. Claim 1 is drawn to a composition comprising a monoclonal antibody and a cell selected from the group consisting of proNP, NNP, and NP cells, wherein the monoclonal antibody is specifically bound to a RET antigen on one of the recited cell types.

As the Examiner has stated, support for the claimed composition is found in the specification by way of the cell sorting experiments (*see* page 18, line 13 to page 35, line 2). Applicants respectfully assert that the working examples enable the claimed composition and demonstrate its utility. By providing at least one use of the composition, disclosure of other uses are not required.

In view of the working examples, Applicants respectfully assert that the specification fulfills the requirements of §112, first paragraph and respectfully request the Examiner to withdraw the rejection.

Claims 1-2, 4-7, and 12-15 stand rejected under 35 U.S.C. § 112, second paragraph. The Examiner contends the metes and bounds of "RET antigen" cannot be determined. Applicants respectfully traverse.

The metes and bounds of "RET antigen" are defined in the specification at page 7, lines 12-14, which states: "All or part of the sequence of RET may be used as a RET antigen." Thus, a "RET antigen" is all or part of the amino acid sequence that comprises the RET protein. The RET amino acid sequences are expressly incorporated by reference at page 7, lines 9-11. Methods employing all or part of the RET amino acid sequence in the generation of RET antibody are provided at page 7, line 19 to page 11, line 2.

In view of the disclosed definition, RET sequences, and methods, Applicants respectfully assert that the scope of the claim is clear to a hypothetical person possessing

possessing the ordinary level of skill in the pertinent art. Therefore, Applicants respectfully request the Examiner to withdraw the rejection.

Claims 1-2, 4-8, and 12-15 stand rejected under 35 U.S.C. §102(a) as being anticipated by Lo *et al.* 1995. Neuron 15:527-539. Applicants respectfully traverse.

In accordance with §1.48(a), Applicants are preparing the necessary documentation to amend the inventorship in this case to include Liching Lo. New declarations, the required petitions, and the consent of the assignee will be forthcoming. Thus, the Lo *et al.* reference does not constitute publication by another and is not prior art. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection.

Claims 1-2, 4-8, and 12-15 stand rejected under 35 U.S.C. §102(f)/(g). The Examiner contends the Applicants belief that Liching Lo is a co-inventor of the claimed subject matter indicates that the instant inventive entity did not invent the claimed invention. Applicants respectfully traverse.

As stated above, the documents required under §1.48(a) to include Liching Lo as an inventor are forthcoming. Therefore, Applicants respectfully request that the rejection be held in abeyance.

Claim 8 stands rejected under 35 U.S.C. §102(b) as being anticipated by Stemple *et al.* 1992. Cell 71:973-985. The Examiner contends that Stemple *et al.* disclose a substantially pure population of cells having the developmental potential of the instant cell populations. Applicants respectfully traverse.

Claim 8 is directed to a substantially pure population of neural crest derived neural progenitor cells selected from the group consisting of multipotent proneural progenitor (proNP) cells, nonneuronal progenitor (NNP) cells and committed neuronal progenitor (NP) cells. "Substantially pure" is defined at page 11, lines 4-6 as: "at

least about 50% of the cells present after sorting are either neural progenitor cells or neurons...." A neural progenitor cell is defined at page 11, lines 7-9 as:

> one or a mixture of cell types, including proneuronal progenitors (proNP), nonneuronal progenitors (NNP), and neuronal progenitors (NP) cells. All of these cell types express RET antigen as demonstrated by the binding of RET antibody and are thus RET^{+}.

The specification does state on page 26, that some of the cells isolated by the method of Stemple *et al.* using antibody 192Ig are NP cells. However, the NP cells isolated by the method of Stemple *et al.* do not constitute a "substantially pure" population. As described on page 26, line 16, neural crest cells isolated using antibody 192Ig directed against the low affinity NGF receptor ($p75^{LNGFR}$) are 6.5% NP cells. In contrast, the cell population obtained with RET antibody is about 50% NP cells (*see* page 26, lines 17-19).

As the Examiner is aware, to anticipate a claim a reference must teach each and every element of the claim. For the reasons set forth above, the NP cell population of Stemple *et al.* is not "substantially pure". Thus, Stemple *et al.* do not teach at least one element of Claim 8 and can not anticipate the claimed invention. Therefore, Applicants respectfully request the Examiner to withdraw the rejection.

Claims 1 and 2 stand rejected under 35 U.S.C. §102(b) as being anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious in view of Martucciello *et al.* The Examiner contends that the claims appear to be directed to an anti-RET monoclonal antibody which is disclosed by Martucciello *et al.* The Examiner further contends that the claims recite an intended use of the monoclonal antibody that can not be accorded any weight in determining patentability. The Examiner requires factual evidence of a difference between the disclosure of Martucciello *et al.* and the claimed invention. Applicants respectfully traverse.

As described above, Applicants respectfully submit that the Examiner has misinterpreted the scope of Claims 1 and 2. Claim 1 has been amended for clarity and

is drawn to a composition comprising a monoclonal antibody that is bound to a RET antigen on a cell selected from the group consisting of proNP, NNP, and NP cells. Therefore, Claims 1 and 2 are not limited to a monoclonal antibody and do not recite an intended use of the monoclonal antibody. Rather, the claims are drawn to a composition comprising a monoclonal antibody that is specifically bound to a RET antigen on a cell.

In view of the scope of Claims 1 and 2, Applicants respectfully assert that Martucciello *et al.* do not teach or suggest the claimed composition. Martucciello *et al.* report an analysis of RET protein expression by immunohistochemical staining of the ganglia of normal colon and the colon of Hirschsprung's Disease (HD) patients. As defined by the McGraw-Hill Encyclopedia of Science & Technology (Exhibit A), a ganglion is a group of nerve cell bodies, usually located outside the brain and spinal cord. A nerve cell body (*see* Exhibit B) is a component of a neuron or nerve cell and contains the nucleus and usual cytoplasmic organelles. Thus, a ganglion contains the cell bodies of neurons, which are terminally differentiated cells and are not neural progenitor cells, such as, the claimed proneuronal progenitors (proNP), nonneuronal progenitors (NNP), or committed neuronal progenitors (NP). Martucciello *et al.* teaches that RET is expressed on the nerve cell bodies of neurons but do not teach or suggest that RET is expressed on other cell types. Therefore, Martucciello *et al.* do not teach each and every element of the claimed invention and do not anticipate.

Applicants also respectfully assert that Martucciello *et al.* do not render the claimed invention obvious. To establish a *prima facie* case of obviousness there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; there must be a reasonable expectation of success; and the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's

disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) M.P.E.P. §2143.

As outlined above, Martucciello *et al.* do not teach or suggest that RET is expressed on the claimed neuronal progenitor cells or any other cell type. Therefore, Martuciello *et al.* do not provide a suggestion or motivation to practice the claimed invention, do not provide a reasonable expectation of success, and do not teach or suggest all the claim limitations. Therefore, Applicants respectfully assert that Martuciello *et al.* do not support a conclusion of obviousness.

In view of these remarks, Applicants respectfully request the Examiner to withdraw the rejections.

Claim 8 stands rejected under 35 U.S.C. § 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious in view of Vescovi *et al.* Applicants respectfully traverse.

Vescovi *et al.* report the continual proliferation of EGF-dependent progenitor cells isolated from mouse and human embryonic central nervous systems. These cells differ in several respects from the population of neural progenitor cells of Claim 8. For example, Vescovi *et al.* do not report that their EGF-dependent cells are substantially pure. Vescovi *et al.* do not characterize their cultured cells, nor do they indicate that the EGF-dependent cells were specifically enriched. Therefore, it is improper to conclude that the cells of Vescovi *et al.* are substantially pure. Vescovi *et al.* do state that "Neurospheres could be dissociated and re-plated as single cells" but this does not indicate that individual cells were cloned. Rather, Vescovi *et al.* are stating that the neurospheres were dissociated such that individual cells were distributed across the tissue culture surface.

In another aspect, the cells of Vescovi *et al.* are derived from the embryonic diencephalon and mesencephalon, are EGF-dependent, and differentiate into cells that express neuronal or glial specific antigens.

> To assess the ability of EGF-dependent cells to continuously generate neurons and astrocytes, "2^{nd}- through 6^{th}-generation" neurospheres were

> pulse-labelled with 2 μM Bromodeoxyuridine (BrdU) for 24 hours, differentiated in the presence of 2% serum for 7 days and eventually process for indirect immunocytochemistry. Cells were found which simultaneously labelled with both antisera raised against neuronal - (NSE, MAP-2) or glial-specific antigens (GFAP) and antibodies recognising BrdU.

In contrast to the cells of Vescovi *et al.*, the neural progenitor cells of Claim 8 are substantially pure, are derived from neural crest and comprise three functionally distinct subsets: NP, NNP, and proNP. Each of the claimed neural progenitor cells are demonstrated to differentiate, respectively, into: i) neurons; ii) nonneuronal cells; and iii) neurons, glial cells, and unidentified nonneuronal cells (*see* page 23, line 1 to page 25, line 19). Thus, none of the claimed neural progenitor cells only differentiate into neuronal and glial cells. Therefore, Applicants respectfully assert that the claimed neural progenitor cells are distinct from EGF-dependent cells of Vescovi *et al.* in regards to their origin, differentiation potential, and purity.

In view of these remarks, Vescovi *et al.* do not teach or suggest each and every element of the claimed invention and, as such, do not anticipate and do not support a conclusion of obviousness. Therefore, Applicants respectfully request the Examiner to withdraw the rejection.

Claim 8 stands rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious in view of Reynolds *et al.* Soc. Neurosci. Abstr. 18:1107, Abstract 467.3, 1992. Applicants respectfully traverse.

Reynolds *et al.* report the presence of EGF-responsive progenitor cells in the murine and human embryonic central nervous system. Differences between the cells of Reynolds *et al.* and the cells of Claim 8 can be summarized as follows. First, Reynolds *et al.* do not report that the cultured EGF-responsive progenitor cells are substantially pure. Reynolds *et al.* do not characterize their cultured cells, nor do they indicate that the EGF-responsive cells were specifically enriched. Reynolds *et al.* do state that "floating spheres were dissociated and replated at low density as single cells".

However, Applicants respectfully assert this means that the cells of the floating spheres were dissociated and replated such that individual cells were distributed across the tissue culture surface. Reynolds *et al.* are not reporting that individual cells were cloned and isolated.

Second, the cells of Reynolds *et al.* are derived from the embryonic cortex, striatum, and cerebellum rather than the neural crest. Third, the EGF-responsive cells only differentiate into neurons and, possibly, astrocytes:

> When spheres were plated onto poly-L-ornithine-coated glass coverslips, cells migrated from the central core, adopting the morphology of neurons and astrocytes. The presence of neurons was confirmed with antisera directed against human neuron-specific enolase.

In contrast, the neural progenitor cells of Claim 8 are derived from neural crest, and comprise three functionally distinct subsets, NP, NNP, and proNP, which differentiate, respectively, into: i) neurons; ii) nonneuronal cells; and iii) neurons, glial cells, and unidentified nonneuronal cells (*see* page 23, line 1 to page 25, line 19). Thus, none of the claimed neural crest derived progenitors only differentiate into neurons and astrocytes, which are the products of EGF-responsive progenitor differentiation. Furthermore, the claimed neural progenitor cultures are specifically enriched and demonstrated to be substantially pure.

Therefore, Applicants respectfully assert that the cells of Reynolds *et al.* are distinct from the cells of Claim 8 with respect to their origin, physiology, differentiation potential and purity. Therefore, Reynolds *et al.* do not teach or suggest the claimed invention and can not anticipate or render the claimed invention obvious.

In view of these remarks, Applicants respectfully request the Examiner to withdraw the rejection.

Claim 8 stands rejected under 35 U.S.C. § 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as being obvious in view of Boss *et al.* (U.S. Patent No. 5,411,883). Applicants respectfully traverse.

Boss *et al.* report a method for the isolation and proliferation of neuron progenitors cells. The cells of Boss *et al.* differ from the cells of Claim 8 as follows. First, the progenitor cells of Boss *et al.* are derived from the ventral mesencephalon. Second, the progenitor cells of Boss *et al.* are not substantially pure.

Contrary to the Examiner's assertion, Boss *et al.* do not characterize their cultured cells, nor do they indicate that the neural progenitor cells were specifically enriched. The Examiner has asserted that "different methods of isolation are not dispositive of the issues as the process of making a product does not serve to distinguish the same product made by another method." In response, Applicants respectfully assert that the cell populations of Boss *et al.* and the claimed invention are distinct because Boss *et al.* do not employ a specific enrichment step and do not employ cells of the appropriate lineage that are required to produce the claimed cell population. Therefore, Applicants respectfully submit it is improper to conclude that the cultures of Boss *et al.* are the claimed "substantially pure" neuronal progenitor cells.

In view of the absence of a teaching or suggestion in regards to the claimed substantially pure population of neural progenitor cells, Applicants respectfully assert that Boss *et al.* do not anticipate the claimed invention and do not support a conclusion of obviousness. Therefore, Applicants respectfully request the Examiner to withdraw the rejection.

Claims 1-2 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hesketh in view of Martucciello *et al.*, Campbell *et al.*, Harlow *et al.*, and Maurer *et al.* for reasons of record. The Examiner contends the claims are directed to a monoclonal antibody and recite an intended use of the monoclonal antibody. Applicants respectfully traverse.

As previously stated, Claim 1 is drawn to a composition comprising a monoclonal antibody bound to a RET antigen on a neuronal progenitor cell, a

nonneuronal progenitor cell or a committed neuronal progenitor cell. The claimed composition is not limited to monoclonal antibody.

Hesketh reports that RET is expressed in the developing central and peripheral nervous systems, and the excretory systems of mice. Hesketh also reports that proto-oncogene forms of RET are expressed in human medullary thyroid carcinomas (MTCs) and pheochromocytomas and in neuroblastoma cells after induction of differentiation (*see* page 241). Hesketh does not teach or suggest the claimed composition comprising a monoclonal antibody bound to a RET antigen on a proNP, NNP, or NP cell.

None of the secondary references add substantially to the disclosure of Hesketh. As summarized above, Martucciello *et al.* discloses a RET monoclonal antibody bound to neurons. Campbell report methods of antibody purification and monoclonal antibody production. Harlow *et al.* report methods of antibody induction. Maurer *et al.* report methods of inducing antibodies and antigen presentation.

Therefore, none of the references, either alone or in combination, teach or suggest the composition as claimed. Moreover, the references do not teach or suggest proNP, NNP, or NP cells or that these cells are RET positive. In view of the requirements for establishing a *prima facie* case of obviousness summarized above, Applicants respectfully submit that the references do not teach or suggested the claimed invention, do not provide a reasonable expectation of success, and do not teach each and every element of Claims 1 and 2.

In view of these remarks, Applicants respectfully submit that the references do not support a conclusion of obviousness and respectfully request the Examiner to withdraw the rejection.

Claims 1-2, 4-8, and 12-15 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lo *et al.* (Perspectives Dev. Neurobiol. 2:191-201, 1994), Stemple *et al.* (Dev. Biol. 159:12-23, 1993), Stemple *et al.* (Cell 71:973-985, 1992), and Martucciello *et al.* for reasons of record. Applicants respectfully traverse.

In the Amendment filed July 19, 1998, Applicants argued that the references do not teach or suggest the claimed invention and, therefore, do not provide a reasonable expectation of success in reaching the claimed invention. In further support of this position, Applicants respectfully point out that the instant application is the first disclosure that RET is expressed by neural crest derived multipotent neuronal progenitor cells, nonneuronal progenitor cells, and committed neuronal progenitor cells. These cell types are distinguished by their differentiation, respectively, to: i) neurons, ii) nonneuronal cells, and iii) neurons, glial cells, and unidentified nonneuronal cells. In addition, novel methods for the enrichment of these cell types are disclosed.

The prior art, as exemplified by Lo *et al.*, state on page 199, right column, last paragraph that: "...*c-ret* provides valuable markers for very early stages in neural crest cell lineage diversification." However, Lo *et al.* do not teach or suggest the existence of the disclosed cell types, that they are RET positive or methods for their enrichment. Lo *et al.* propose a scheme of uncommitted neural crest cell differentiation in Figure 6; however, when viewed in light of the specification Figure 6 is in error. Specifically, Figure 6 indicates that glial progenitors are *c-ret* negative. As seen on the right side of the figure, Lo *et al.* do not label the glial progenitor cell as expressing *c-ret*. The specification clearly demonstrates that this is incorrect. At page 32, lines 17-19, the committed neuronal progenitor cells, which differentiate into glial cells, are *c-ret* positive. Therefore, the disclosure of Lo *et al.* is not enabling, teaches away from the claimed invention, and is at best an invitation to experiment.

None of the secondary references relate to the claimed cell populations and enrichment methods and, as such, do not correct the deficiencies of Lo *et al.* Briefly, Stemple '93 teach developmental heterogeneity in neural crest cells and methods for their analysis. Stemple '92 is limited to fluorescence activated cell sorting. Martucciello *et al.* report a monoclonal antibody bound to a RET antigen on a neuron.

In view of these remarks, Applicants respectfully submit that none of the references, either alone or in combination, meet the requirements for establishing a

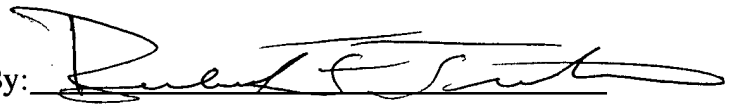
prima facie case of obviousness. Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned attorney.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

By: 
Richard F. Trecartin
Reg. No. 31,801

Four Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187
(415) 781-1989